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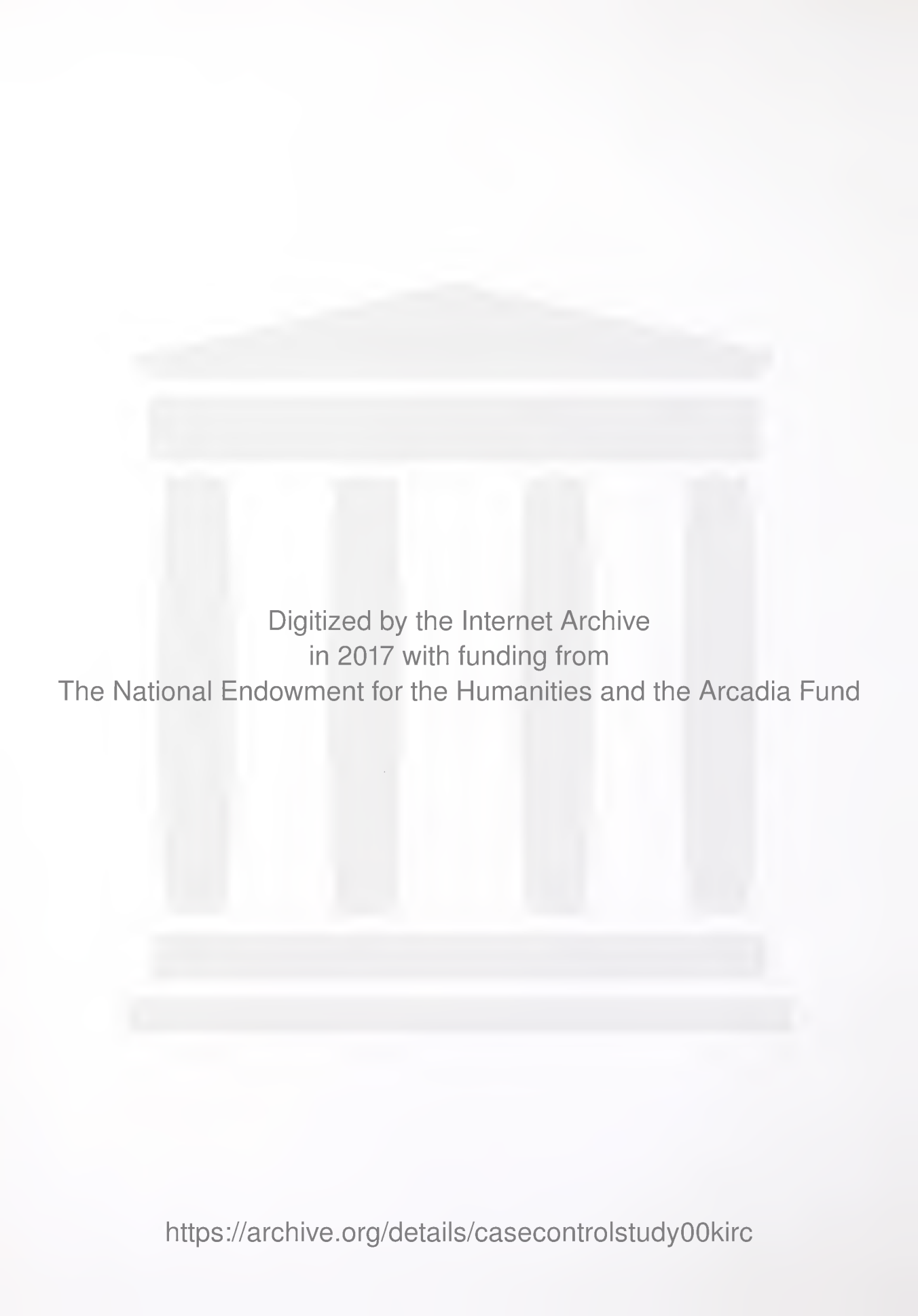

A CASE-CONTROL STUDY OF EPIDEMIOLOGIC PARAMETERS RELATING TO HODGKIN'S DISEASE IN BRAZIL

by

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Louis Vaught Kirchhoff

March 1, 1977

Dedication

Dedico esta tese a meus pais, que sempre têm ajudado tanto, a Karen, quem fêz a metade do trabalho a pesar das condicões em que se encontrava, e à pequena Alícia, quem acompanhou a gente durante o tempo todinho.

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Abstract

A number of epidemiologic variables were investigated in a case-control interview study, conducted in São Paulo, Brazil, of 70 Hodgkin's disease patients, 70 control subjects matched for age and sex, and 128 siblings of the patients. In this group of Hodgkin's disease patients, a high percentage of total cases among children, with a high sex ratio, a relative predominance of the mixed cellularity and lymphocytic depletion histological subtypes, and a unimodal age-specific incidence curve with the highest rates among the elderly, were found.

When the matched controls were used as the comparison group, high socioeconomic status, as measured by current occupation and level of education, was found to be associated with an increased risk for Hodgkin's disease ($P = 0.001$). On the basis of the case-sibling comparison, an association between prior tonsillectomy and risk for this disorder was found ($P = 0.03$), and the relative risk for Hodgkin's disease among tonsillectomized persons as compared to individuals who had not had the operation was 2.7, with a 95% confidence interval of 1.1 → 6.6. When this comparison was repeated for large and small sibships, an increased risk among tonsillectomized persons was found only in sibships of size six or greater.

Other variables, including marital status, birth order, occupational exposure, prior use of amphetamines or diphenylhydantion, intensity of exposure to children and history of viral illnesses were not found to be determinants of risk for Hodgkin's disease.

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Tables and Figures

I. Introduction

Hodgkin's disease is a disorder of unknown etiology with a world-wide distribution. In recent decades the epidemiology of Hodgkin's disease has been studied intensively. The descriptive epidemiologic aspects of the disorder which relate to incidence and distribution as functions of age, sex, race and histologic subtype have been well-characterized in the industrialized nations and to a lesser extent in several of the developing countries. Considerable international variation in the pattern of occurrence of Hodgkin's disease has been observed. Other epidemiologic and family considerations have been investigated in a variety of settings in an effort to identify those factors which are associated with an increased risk for developing the disease. To date, all research of this nature has been conducted in the developed countries.

The objective of the present investigation was to identify risk factors for Hodgkin's disease in a case-control interview study of patients with this disease in São Paulo, Brazil. In view of the fact that the descriptive epidemiology of Hodgkin's disease in Brazil is considerably different from that of the developed countries, it was anticipated that other aspects of the epidemiology would show a variation as well, and that the international comparison of these parameters would provide useful insight into the etiology and development of Hodgkin's disease.

II. Description of Hodgkin's Disease

In 1832 Thomas Hodgkin(1) published his classic paper, "On Some Morbid Appearances of the Absorbent Glands and Spleen," in which he described seven patients who had died with lymph node and splenic enlargement, several of whom are thought to have had the disorder which now bears his name. During the decades following this report, interest in this enigmatic disorder grew and the histology of the lesions of Hodgkin's disease was studied intensively by many of the renowned pathologists of that period, including Virchow, Langhans, Greenfield and Cohnheim. In 1902 Reed(2) and Sternberg(3) described in detail the virtually pathognomonic giant cell which bears their names.

As the interest in Hodgkin's disease became widespread during the latter half of the 19th century, a controversy arose regarding the basic nature and etiology of the disorder. Hodgkin(1) considered the disease to be a hypertrophic disease of the lymphatic system. Reed(2) was convinced that it was the result of an infectious process, while Sternberg(3) thought it was a variant of tuberculosis. In 1931 Warthin(4) argued that it was a neoplastic disease, and today, although it is classified as one of the neoplasms of the lymphatic and hemopoietic tissues, the controversy surrounding the nature of the disorder and its etiology remains unsettled.

Any theory of causation of Hodgkin's disease must account for the widely varying characteristics of the disorder. The diversity of clinical and histological pictures, and the varying anatomic predilections of some of the histological subtypes are difficult to

explain. Moreover, although the disease is often accompanied by a marked histopathologic inflammatory reaction and systemic symptoms suggestive of an infective process, the intensive search for an infectious etiologic agent has proved fruitless. A perplexing picture also is presented by those aspects of the disease which suggest neoplasia. The usual rarity of the putative neoplastic Reed-Sternberg cell in Hodgkin's disease tissue and the fact that this cell is found in other disorders which are not neoplastic are two aspects of the disorder which do not conform to the conventional definition of neoplastic disease(5). The matter is confounded further by a peculiar epidemiology in which the marked international variation in age-specific incidence rates is correlated with the level of socioeconomic development.

Hodgkin's disease is distributed world-wide and has an annual incidence rate of approximately three per 100,000, though this figure varies considerably as a function of geography, age, sex and race. Considerably more cases are observed among males than females, with an overall sex ratio of roughly two.

The minimum requirement for the pathologic diagnosis of Hodgkin's disease is the presence of the characteristic giant cells of the Reed-Sternberg type in an appropriate histological setting. The most reliable characteristics of these cells are double or multiple nuclei and large inclusion-like nucleoli, but the variable number and the morphologic diversity of these cells, viewed against a protean background of inflammatory proliferation, fibrosis and necrosis, challenge the thesis that Hodgkin's disease, as presently

defined, is a single entity.

At present there are four internationally accepted histopathologic classifications for Hodgkin's disease. Listed in order of increasingly unfavorable prognosis they are nodular sclerosis, lymphocytic predominance, mixed cellularity and lymphocytic depletion. Mediastinal lesions are more frequently of the nodular sclerosis subtype, whereas abdominal and cervical or supraclavicular disease is more commonly of the lymphocytic predominance and mixed cellularity classifications, all of which suggest that the four subtypes are realistic sub-groupings of the disorder with respect to prognosis and pathogenesis.

The presenting symptoms and post-diagnostic manifestations of Hodgkin's disease are highly varied and affected by the various therapies employed to combat the disease. Typically, the patient observes the presence of a painless, enlarging, rubbery mass, most commonly in the neck, but occasionally in the axilla or inguinal region. In some cases the presenting symptom is a persistent and unexplained low-grade fever, accompanied by night sweats, fatigue and weight loss. Less commonly a generalized pruritis accompanies these symptoms, and very occasionally it is the presenting complaint.

The clinical course of Hodgkin's disease is also quite variable. Commonly, over a period of months or years, the disease spreads to lymph nodes adjacent to the initial site of the tumor. If the process is not controlled by therapy, extranodal involvement follows hematogeneous dissemination of aberrant cells. Intrathoracic problems with compression of airways or great veins, pulmonary parenchymal involvement, invasion of the sternum, clavicle, ribs or

vertebrae with mixed lytic and blastic lesions, hepatic infiltration associated with splenic involvement and neuropathies secondary to nerve compression are among the common elements of uncontrolled Hodgkin's disease. Hematologic abnormalities frequently include anemia and a leukemoid reaction which may be confused with intercurrent chronic myelogeneous leukemia, especially in the untreated patients. Furthermore, immunologic abnormalities are observed in Hodgkin's disease patients and most commonly include a defect in delayed hypersensitivity to antigens to which the patients previously have been exposed, a delayed reaction to new antigens and an inability to synthesize migratory inhibition factor. This depression of cell-mediated immunity has been observed among both treated and untreated patients, and in general, the more advanced the stage of the disease, the more complete is the loss of these elements of the immune response.

Until recently Hodgkin's disease was viewed as a uniformly fatal disorder with a variable rate of progression. Considerable progress has been made in recent years in the treatment of Hodgkin's disease with radiotherapy and to a lesser extent with chemotherapy. At present, patients with localized disease treated with total lymphoid radiotherapy have an estimated five-year survival rate of 90%, and in fact some of these patients may be cured. The rates for patients with more widespread disease diminishes as the number of involved sites increases, and for those with disseminated disease involving non-lymphatic tissues, a five-year survival rate of approximately 30% has been achieved in those medical centers where meticulous staging and judicious use of combined radiotherapy and chemotherapy are employed.

III. Review of the Literature

a. Geographic Pathology

There is considerable international variation in the overall and age-specific incidence for Hodgkin's disease. Although incidence rates gradually increase after age 45 in all countries studied, the rates for the younger age groups vary in a pattern which suggests the grouping of countries by level of socioeconomic development. In most industrialized nations the incidence curve is bimodal, with an early peak among young adults and a second among the elderly(6). This age distribution is illustrated by the 1960-68 data for Connecticut presented in Figure 1. The exception to this pattern is Japan, where the curve is unimodal and lacks the early peak.

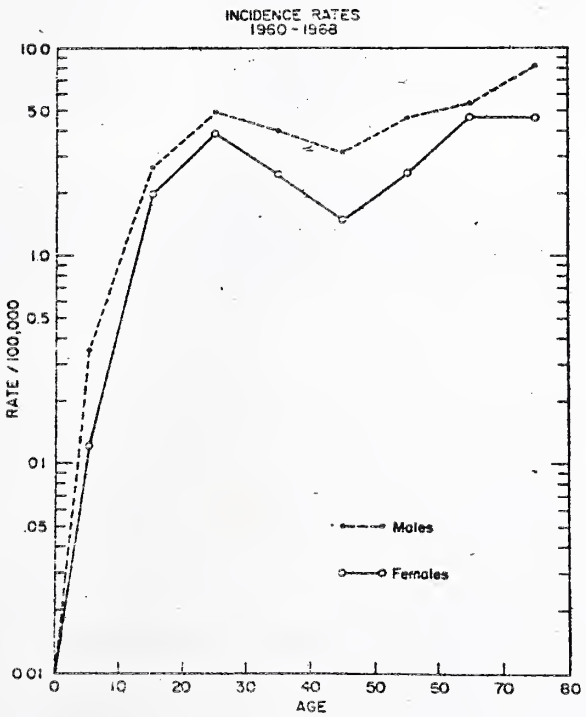

Figure 1. Age-specific incidence rates of Hodgkin's disease for males and females in Connecticut, 1960-68 (7).

In developing regions such as Latin America, the early peak in the incidence curve is less pronounced and there is a relatively high rate among children, especially males. In addition, the proportion of patients with the histological subtypes associated with less favorable prognoses is elevated in comparison to the industrialized regions(8). This type of incidence pattern is shown in the curves for Chile and Recife, Brazil, presented in Figures 2 and 3.

Correa and O'Conor(9) have defined three principal epidemiologic patterns of Hodgkin's disease occurrence:

> Type I (Developing countries in the tropics): In these areas Hodgkin's disease is unusually frequent in children, does not show an incidence peak in young adults and has a relatively high sex ratio.
>
> Type II (Some developing nations in sub-tropical and tropical regions): A high proportion of cases in children and a rise in frequency in young adults, with a comparatively high proportion of mixed cellularity and lymphocytic depletion subtypes in these age groups.
>
> Type III (Developed nations): Hodgkin's disease is relatively rare in children and the overall distribution displays the classic bimodality of age-specific rates, with a predominance of the nodular sclerosis subtype and a high sex ratio among the elderly.

In addition to the international variation in epidemiologic patterns, differences have also been observed between regions within the same country. Correa(8) reported that the distribution in rural Norway was Type II, whereas in the urban centers it was Type III. Similarly, in the United States during the 1949-54 period the pattern of occurrence of Hodgkin's disease in the eleven contiguous Southern states was Type II, while in the rest of the country it was Type III(10). Secular changes in the pattern of occurrence also have been observed as the level of economic development has increased. Data collected

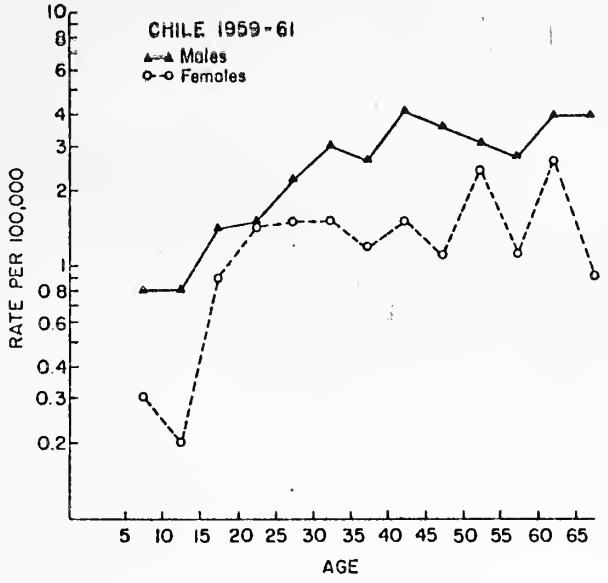

Figure 2. Age-specific incidence of Hodgkin's disease in Chile, 1959-1961 (8).

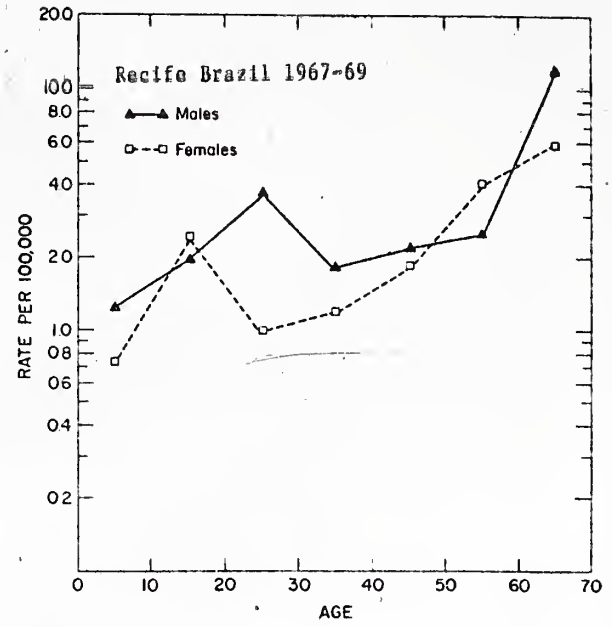

Figure 3. Age-specific incidence of Hodgkin's disease in Recife, Brazil, 1967-1969 (8).

by Shimkin(11) for the 30 years ending in 1951 showed that the overall pattern for the United States changed from Type II to Type III during this period.

Only limited data on the epidemiology of Hodgkin's disease in Brazil is available in the literature. In addition to the incidence data for Recife presented above (Figure 2), Correa(8) presented sex ratio and histologic subtype figures from Recife and São Paulo for 1961-70. These data are shown in Tables 1 and 2, along with data from the present study. Information from Columbia, Argentina and Connecticut are included for comparison.

More recent data from the São Paulo Tumor Registry(12) for 1969-72 are presented in Table 3, along with data from the present study. Incidence rates have not been calculated from these figures because the Registry may not be complete and also because the population denominators are not defined.

The data from the literature presented up to this point indicate that the epidemiologic pattern for urban Brazil is Type II. This classification is supported by the relatively high proportion of total cases among children, with a high sex ratio in this group, the bimodal incidence curve with peaks among young adults and the elderly, and the relatively high proportion of the histologic subtypes associated with a poor prognosis.

Table 1. Hodgkin's disease in Latin America and Connecticut. Sex ratio by age interval, and histologic subtype ratios (8).

Location (year)	Sex ratio: males/females			
	0-19 yrs old	20-49 yrs old	≥50 yrs old	ratio NS+LP/MC+LD*
Recife, Brazil (1961-70)	2.3	2.1	1.4	1.4
São Paulo, Brazil (1961-70)	3.7	2.3	1.9	0.6
Present Study, São Paulo, Brazil (1976)	3.8	2.0	2.3	0.9
Bogota, Columbia (1955-70)	3.0	3.4	1.4	0.6
Buenos Aires, Argentina (1957-70)	1.7	1.5	2.3	0.6
Connecticut (1950-68)	1.1	1.5	1.5	1.4

*NS = Nodular sclerosis, LP = Lymphocytic predominance, MC = Mixed cellularity, LD = Lymphocytic depletion

Table 2. Hodgkin's disease in Latin America and Connecticut. Number of cases and percent distribution by histologic subtype and sex (8).

Location (year)		Males				Females				Number of cases		
		NS*	LP	MC	LD	NS	LP	MC	LD	Mas.	Fem.	Total
Recife, Brazil (1961-70)	N°	19	28	28	13	15	13	13	7	88	48	136
	%	22	32	32	15	31	27	27	15	65	35	100
São Paulo, Brazil (1961-70)	N°	16	17	45	9	18	1	23	2	87	44	131
	%	18	19	52	10	41	2	52	4	66	34	100
Present Study, São Paulo, Brazil (1976)	N°	13	12	21	4	2	6	7	5	50	20	70
	%	26	23	42	9	10	32	32	26	71	29	100
Bogota, Columbia (1955-70)	N°	19	31	81	16	9	10	25	9	147	53	200
	%	13	21	55	11	17	19	47	17	74	26	100
Buenos Aires, Argentina (1957-70)	N°	50	78	154	31	57	27	79	25	313	188	501
	%	16	25	49	10	30	14	42	13	62	38	100
Connecticut (1950-68)	N°	82	42	65	21	76	7	52	22	210	157	367
	%	39	20	31	10	48	4	33	14	57	43	100

*NS = Nodular sclerosis, LP = Lymphocytic predominance, MC = Mixed cellularity, LD = Lymphocytic depletion

Table 3. Hodgkin's disease in São Paulo, Brazil. Percent distribution by age and year, and sex ratios.

Data source		Age interval (years)									
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70+	Total	Sex ratio
Sao Pãulo Tumor Registry 1969	N°	18	28	33	35	22	22	26	8	192	2.0
	%	9	15	17	19	11	11	14	4	100	
1970	N°	14	26	41	35	33	23	25	7	204	1.9
	%	7	13	20	17	16	11	12	4	100	
1971	N°	21	36	34	33	19	18	14	4	179	2.2
	%	12	20	19	18	11	10	8	2	100	
1972	N°	11	24	41	32	33	17	11	9	178	1.7
	%	6	13	23	18	19	10	6	5	100	
Total for 1969-72	N°	64	114	149	135	107	80	76	28	753	2.0
	%	8	15	20	18	14	11	10	4	100	
Present Study, São Paulo 1976	N°	15	14	15	7	8	10	0	1	70	2.0
	%	21	20	21	10	11	14	0	1	100	

b. Modifiers of Host Immunocompetence

1. Tonsillectomy

During the past six years there have been a number of studies done on the prevalence of tonsillectomy history among patients with Hodgkin's disease. Research on this subject has its origins in previous work of several authors who approached the broader question of the possible effect of lymphatic tissue ablation, either by appendectomy or tonsillectomy, on the incidence of cancer. In 1966 McVay(13), in an autopsy study, reported that the prevalence of previous appendectomy was significantly greater among cancer patients, especially those with colonic lesions, than among unmatched control patients who had died of vascular disease. McVay hypothesized that the lymphatic tissue of the appendix acts as a protective device against infective agents which may initiate malignant change in the gastrointestinal tract and other sites, and suggested that further studies include similar work in relation to tonsillectomy. Bierman(14) conducted a similar study in which patient interviews and autopsy data were utilized and found an increased prevalence of previous appendectomy in a mixed cancer group in comparison to controls with vascular disease. The most significant rates were found in the colonic, breast and ovarian cancer groups. He also reported a higher rate of appendectomy among the 57 Hodgkin's disease patients in the study.

Gross(15) interviewed 300 cancer patients and 200 unmatched controls and compared their rates of appendectomy and tonsillectomy. He reported no significant difference between the two groups for

either operation, although he did observe that the cancer patients had had their procedure significantly later in life and suggested that the surgical removal of lymphatic tissue may be the final insult to an already failing immunologic capacity. Only four Hodgkin's disease patients were included in this study.

In 1968 Hyams and Wynder(16) reviewed the conflicting studies done up to that time, including a British study by Howie and Timperly(17) which failed to demonstrate a higher rate of appendectomy in any specific cancer group, and presented the results of their own interview study of over 1,300 patients and controls. Their analysis showed that males with Hodgkin's disease had a significantly higher prevalence of appendectomy than the unmatched control group, although nearly four-fifths of the Hodgkin's disease patients had not had the operation. No other significant differences in appendectomy prevalence were demonstrable in males. Among women, the large bowel and breast cancer groups showed significantly higher rates when compared to certain controls, but not to others. Hyams and Wynder concluded that the hypothesized relationship between appendectomy prevalence and cancer cannot be accepted and pointed to the difficulty of controlling for a variety of epidemiologic factors as the cause of the disparity of the results from previous studies.

The question of a possible relationship between tonsillectomy and Hodgkin's disease was touched upon by Miller(18), who examined the Hodgkin's disease mortality by single year of age for the United States for 1950-59 and noted that, in contrast to other childhood cancers, the age-specific incidence of Hodgkin's disease among

children rises rapidly during the age period of seven to ten years. It is during this period when the lymphatic system reaches the peak of its development and begins a gradual regression. Miller suggested that faulty regression of the lymphatic system may play a role in the genesis of the disorder, and recommended that an epidemiologic study of the relationship between Hodgkin's disease and prior medical history relating to the lymphatic system, particularly of the oropharynx, be undertaken.

This issue first was approached directly by Vianna et al.(19) in a retrospective case-control study of 109 Hodgkin's disease patients. They reported that Hodgkin's disease cases and controls differed significantly in their rates of prior tonsillectomy and estimated the relative risk of developing Hodgkin's disease among tonsillectomized persons to be 2.9 times that of those who had not had the operation. Vianna et al. called attention to the role of the tonsilar lymphatic tissue as a barrier to infective agents, and suggested that surgical ablation of the tonsils in some people predisposes to Hodgkin's disease through a diminution of the function of this barrier. However, there was no increase in the frequency of the primary lesion being in the cervical nodes among the Hodgkin's disease patients with prior tonsillectomy, as might be expected under the "barrier hypothesis," which suggests that an immunologic mechanism of tumor formation might account for the increased relative risk. Also, while Vianna et al. acknowledged that Hodgkin's disease and tonsillectomy incidence rates previously had been shown to be positively correlated with socioeconomic status(20), the significance of the study results was not discussed in light of this association.

The method of control selection used by Vianna et al. was criticized by Player(21), who suggested that a more appropriate comparison group would consist of patients with severe tonsillitis who had not had the operation.

Following the publication of this study by Vianna et al. a number of reports dealing with Hodgkin's disease and tonsillectomy appeared in the literature. Ruuskanen et al.(22) did a retrospective study of 106 Finnish Hodgkin's disease patients and controls and failed to confirm an association with tonsillectomy or appendectomy. They also reported that the resistance to infection, as measured by the frequency of the common cold or tonsillitis, was not significantly different in the Hodgkin's disease patients prior to the diagnosis of the disease. The issue was explored further by Johnson and Johnson(23), who studied a series of 174 Hodgkin's disease patients from the Eastern United States using age- and sex-matched siblings as controls. Their findings did not support the hypothesis that tonsillectomy predisposes to Hodgkin's disease. Cole et al.(24) and Shimaoka et al.(25) criticized the analysis presented by Johnson and Johnson and pointed out that their restriction of the study group to the 84 Hodgkin's disease patients for whom a like-sex and age-matched sibling could be found was inappropriate. They contended that the total patient group and all the siblings interviewed should have been included in the analysis which then would have shown a significant association.

In a study done in France, Teillet et al.(26) reviewed the tonsillectomy histories of 225 Hodgkin's disease patients and 307 normal controls and found no difference in rates between the two

groups, nor was there a correlation between prior tonsillectomy and any particular initial site of detection of Hodgkin's disease.

In 1973 Newell(27) and his collaborators reported the results of a case-control retrospective study done among living Hodgkin's disease patients in Louisiana and California. Controls were matched for age, race, sex and socioeconomic status, and the data obtained did not confirm tonsillectomy or appendectomy as a risk factor in Hodgkin's disease. The authors suggested that the matching of patients and controls by socioeconomic status "matched out" the differences in rates which had been interpreted as being significant by other investigators.

The most recent study published on this subject was authored by Gutensohn et al.(28), who compared 136 young adult Hodgkin's disease patients with their 315 siblings and 78 spouses. The siblings and spouses were used as comparison groups in order to control for socioeconomic status in childhood and adulthood, respectively. On the basis of the case-spouse comparison, a significantly elevated relative risk for Hodgkin's disease of 3.1 was found among the tonsillectomized persons in comparison to those who had not had the operation. However, on the basis of the case-sibling comparison, the relative risk was not significantly elevated. The case-sibling analysis was repeated according to sibship size and significantly increased risk for Hodgkin's disease among tonsillectomized individuals was fould only within the sibships of size two. Gutensohn et al. concluded that the relationship between tonsillectomy and Hodgkin's disease is either non-causal or is complex and modified by family size.

In conclusion, the role of tonsillectomy as a risk factor for Hodgkin's disease has not been clarified satisfactorily. The conflicting results of the various investigations described above suggest that unless variables such as socioeconomic status are carefully controlled, interpretation of tonsillectomy data is hazardous. In view of the research done to date, one can conclude that the relationship between tonsillectomy and Hodgkin's disease is not causal, since a majority of patients with the disorder have not had the operation and also because only an extremely small proportion of people who do have their tonsils removed ultimately develop the disease. However, tonsillectomy may affect one's risk for Hodgkin's disease in a manner which is influenced by a number of interrelated factors. The present challenge lies in controlling for these factors so that the effect of tonsillectomy on Hodgkin's disease risk may be assessed.

2. HL-A Antigens

The question of an association between certain antigens of the major histocompatibility system, HL-A, and Hodgkin's disease has been studied by a number of investigators. This work originally was prompted by reports of increased incidence of Hodgkin's disease in first degree relatives of Hodgkin's disease patients, which suggested a genetic basis for the disorder(29). The first investigator to observe an association between an HL-A antigen and Hodgkin's disease was Amiel(30), who reported that the frequency of the 4c antigen was found to be significantly elevated in Hodgkin's disease patients. Subsequent studies have produced conflicting results,

and although significant associations with HL-A1 and HL-A8 appear consistently, the association with the 4c antigen observed by Amiel has been less consistent(31,32,33).

The significance of these findings is not clear. The fact that not all Hodgkin's disease patients have the antigens in question has been interpreted as evidence supporting the hypothesis that HL-A may be one of several systems which affect susceptibility to Hodgkin's disease(34). In summary, the work done to date indicates that the association between HL-A antigens and Hodgkin's disease is complex and most likely is affected by a number of interrelated factors.

c. Correlates of Social Class

Studies have shown that there are a number of epidemiologic factors related to social class which may be associated with an increased risk for Hodgkin's disease. Resolution of the controversies surrounding the role of these factors would be useful in that it could provide at least a partial clarification of the etiology of Hodgkin's disease, and also because it would facilitate the interpretation of data relating to other factors, such as tonsillectomy, which are influenced by social class.

1. Intelligence and Education

Only one study has dealt with the question of intelligence among Hodgkin's disease patients. In 1959 LeShan et al.(35) reported that the mean United States Army Classification Test (AGCT) score for 97 white, enlisted males who developed Hodgkin's disease during World War II was 110.1, while that of the general Army population was 100.0. Also, among 209 Hodgkin's disease patients from the same

population, the greater proportion of prewar occupations were found to be in those occupational groups whose median AGCT scores were the highest. Although the difference between the mean scores is statistically significant, these findings must be viewed with caution since the patients were selected from a restricted segment of the general Army population which constitutes the comparison group. Furthermore, conclusions concerning the general population of patients with Hodgkin's disease are unwarranted because the patients studied here represent a small portion of this larger group.

The question of educational attainment among Hodgkin's disease patients was investigated by Cohen et al.(36), who retrospectively studied 388 white male soldiers with Hodgkin's disease diagnosed during World War II and found that the educational level of the Hodgkin's disease patients was significantly greater than that of a control group of enlisted men, with a risk gradient of 1.9. This finding was confirmed in a study of young, white, adult Hodgkin's disease patients in Boston which showed a significantly higher median level of education among the patients when compared to controls, with a risk gradient for Hodgkin's disease of 2.5 between persons who had reached graduate school and those who had not graduated from high school(B. MacMahon, unpublished data).

2. Socioeconomic Status

The possibility that the risk for Hodgkin's disease is affected by socioeconomic status was investigated by Cohen et al. in the study described above. Analysis of the data from this series of Army Hodgkin's disease patients revealed a significant positive correlation

between risk and socioeconomic status estimated by occupation at the time of enlistment.

In a subsequent study MacMahon(6) examined the standard mortality ratios (SMR's) for Hodgkin's disease in England and Wales for 1949-53, and found elevated SMR's for both sexes among persons of social class I (highest). However, one might suspect that these relatively high SMR's reflect class differences in the accuracy or certification of diagnoses, especially in view of the fact that social class I had elevated SMR's for all lymphomas and leukemias, as well as Hodgkin's disease, during this period. Moreover, similar analysis of the mortality data for the United Kingdom for 1959-63(37) failed to confirm the association between high social class and increased risk for Hodgkin's disease, and no social class correlation was found in a study of patients in whom the disorder was diagnosed in Manchester, England, during 1962-65(38).

This issue was explored indirectly by Vianna et al.(39), who hypothesized that physicians are at an increased risk because of their contact with Hodgkin's disease patients. Review of the death records of male physicians in New York State showed that there were 13 deaths due to Hodgkin's disease during 1960-72, and only 7.2 were expected. Vianna et al. interpreted this as evidence for the existence of a transmissible agent which affects risk for the disorder. In an alternative interpretation the high socioeconomic status of the physicians, and not their patient contact, could be implicated as the risk factor. Subsequently, a similar study of mortality among British physicians during 1951-66 failed to confirm the New York findings(40).

In view of these studies, one must conclude that the issue remains unresolved. The lack of clear resolution of the question may result from the fact that the investigations done to date have looked at a limited aspect of socioeconomic status, namely adult socioeconomic status as measured by occupation approximately at the time of diagnosis. The possibility exists that socioeconomic status acts as a risk determinant only during certain life periods such as childhood or adolescence, and the patient's socioeconomic status during these periods would have to be examined if the influence of socioeconomic status on Hodgkin's disease risk is to be detected.

3. Sibship Size and Birth Order

Evaluation of sibship size as a determinant of risk for Hodgkin's disease is warranted because it is correlated inversely with socioeconomic status and in fact may be that aspect of social class which accounts for the hypothesized association between high socioeconomic status and elevated Hodgkin's disease risk. Gutensohn et al.(28) approached this question in a study of Hodgkin's disease patients from the Eastern United States and found an increasing risk with decreasing sibship size, with a relative risk of 2.0 for only children compared to those who are from sibships of five or greater. These results were questioned by Stoopler et al.(41), who suggested that the comparison group may have been chosen inappropriately, and in addition they reported that their study of 61 white Hodgkin's disease patients aged 15 to 44 years in Atlanta, Georgia, failed to confirm the association of increased risk with decreasing sibship size.

The effect of birth order on risk for Hodgkin's disease has not been evaluated extensively. Among the patients studied by Gutensohn et al.(28), only half the expected number of cases from birth order five or greater were found, which suggests that in large families the later born children are at a relatively low risk for the disease. However, this finding may simply reflect the lower mean socioeconomic status of large families and their underrepresentation in the Hodgkin's disease group, assuming that Hodgkin's disease risk and socioeconomic status are positively associated. Further evaluation of the role of birth order is justified under the hypothesis that the different environments of human exposure experienced by children born early or late in a birth sequence may affect the risk of developing Hodgkin's disease.

4. Marital Status

The marital status of Hodgkin's disease patients has been investigated in two studies. Cohen et al.(36) found that a significantly smaller proportion of the patients they studied were married in comparison to controls. It should be pointed out, however, that this group of patients was found to have a higher socioeconomic status, as measured by pre-service occupation, and because of this would be expected to have a mean age at first marriage higher than that of the control group, thus accounting for the difference. In the study of Hodgkin's disease patients in Manchester, England, Alderson(38) found that the percentage of married patients in his study group and their social class distribution were not significantly different from those of the general population.

5. Occupation

The importance of occupational exposure as a risk factor for Hodgkin's disease first was approached in 1934 in Sweden by Uddstromer(42), who reported no association with occupation in his study of 538 cases. However, there is considerable question regarding the completeness of the census data he used for comparison, and the validity of the findings is suspect because women and children were in the patient group even though they had no job history.

The first subsequent report of an investigation of occupation and Hodgkin's disease appeared in 1967 when Milham(43) described a case-control retrospective study of the occupations of 1,574 white, male, adult patients from New York State who had died of Hodgkin's disease during 1940-63. Although a significant association was found between Hodgkin's disease and occupations which entailed exposure to wood, Milham recognized the problem inherent in working with the limited occupational information on death certificates and also conceded that his method of control selection may have biased the results. No other occupational group was found to have an elevated risk for Hodgkin's disease.

The association of wood exposure with elevated risk for Hodgkin's disease was also found in Washington State in a study done by Petersen and Milham(44) which was similar methodologically to that done in New York. However, a study done by Acheson(45) in the Oxford, England, area, where there is a considerable concentration of woodworking industries, and the one carried out in Manchester, England(38), failed to confirm the association found in the United States.

Other studies of occupational exposure as a risk factor for Hodgkin's disease have been limited to investigations of the comparative Hodgkin's disease mortality for specific occupational groups. In a study of this type carried out by Milham(46), analysis of proportionate mortality due to Hodgkin's disease among male schoolteachers in Washington State showed a significant number of excess deaths in this occupational group. This finding has been interpreted by some investigators as evidence for a transmissible agent in the etiology of Hodgkin's disease(47). This observation was largely refuted by Bahn(48), who pointed out that the proportionate mortality ratio for Hodgkin's disease among schoolteachers appears elevated because their mortality ratios for other causes of death, such as accidents, are lower than those of the general population to which they were compared. An alternative method of analysis suggested by Bahn was done subsequently by Hoover(49), who found that there is no significant excess of Hodgkin's disease mortality among schoolteachers and concluded that transmission of Hodgkin's disease between students and teachers is not a major epidemiologic feature of the disorder.

It is clear at this point that the investigations of occupational exposure as a risk factor for Hodgkin's disease have been inadequate. A definitive study of this issue must include analysis of detailed employment histories of Hodgkin's disease patients and controls if risk from occupational exposure is to be adequately assessed.

In summary, the investigations described above which deal with correlates of social class and risk of Hodgkin's disease have failed to clarify the issues being studied. In reviewing the work done to date it becomes clear that the major methodological challenge lies in the selection of the control groups used for comparison, and considerable attention should be paid to this aspect of the design of future studies. The possibility exists, however, that resolution of the methodological problems relating to comparison groups may not hasten the identification of risk factors, because several causal entities may be represented in the total group of Hodgkin's disease patients, and the inclusion of etiologically diverse Hodgkin's disease patients in study groups may obscure the significance of any given epidemiological factor unless it was common to all causes.

d. Drug Exposure

1. Amphetamines

There have been a number of reports that the use of certain drugs is associated with an increased risk of developing Hodgkin's disease. In the interview study described above, Newell et al.(27) asked patients and controls, matched for age, sex, race and socio-economic status, if they had taken dexedrine or other amphetamines, usually prescribed for weight control, for a period of two months within two years of the onset of their disease, or of the time of the interview in the case of the controls. Analysis of the responses showed a significantly increased prevalence of prior amphetamine use among the patients when compared to the controls, while no differences were found for the use of tranquilizers, thyroid medication,

hormones, narcotics or birth control pills. The difference in amphetamine use was significant for both sexes, for age groups younger and older than 32 years and for patients with the nodular sclerosis and mixed cellularity subtypes.

In a subsequent study, this association was investigated using data collected by the Boston Collaborative Drug Surveillance Program (BCDSP)(50). None of the 315 patients in the Program with a diagnosis of malignant lymphoma, including 183 Hodgkin's disease patients, gave a positive amphetamine-use history, while 10 members of the matched control group of 1,260 people had a positive exposure history. It should be noted, however, that in the BCDSP study the drug use history covered only the months immediately preceding hospitalization, and this limitation may have obscured an existing association.

2. Diphenylhydantoin

There have also been reports of Hodgkin's disease developing in association with the use of diphenylhydantoin, an anticonvulsive agent known to be associated with the induction of pseudolymphoma(51). Hyman and Sommers(52) presented case histories of six patients who developed malignant lymphoma, three of which were Hodgkin's disease, during diphenylhydantoin therapy. Other case history reports have appeared which also suggest this association(53,54). The only epidemiologic study done to date was carried out by Li et al.(55), who found that 1.6 percent of the malignant lymphoma patients in their study had a history of diphenylhydantoin use as compared to 0.6 percent of the control group. Li et al. suggested

that the induction of lymphoma may be related to the immunosuppressive effect of this drug. However, it should be noted that the results were significant only at an eight percent level of confidence ($P = 0.08$) and that only four cases of Hodgkin's disease were among the eight patients with malignant lymphoma who had a history of diphenylhydantoin use.

e. Factors Relating to an Infectious Etiology for Hodgkin's Disease

As discussed above, the basic nature and etiology of Hodgkin's disease are unknown. The clinical and histopathological aspects of this disorder suggestive of an infectious etiology have been observed for over a century. In recent years seroepidemiologic and epidemiologic factors relating to the possible role of an infective agent in the genesis of Hodgkin's disease have been studied intensively.

1. Seroepidemiologic and Virologic Considerations

In recent years the search for an infective agent in Hodgkin's disease has been given impetus by the numerous studies which have implicated viruses as probable causes of various neoplasms in animals(56). To date, however, there is no firm evidence linking Hodgkin's disease or any neoplastic disorder of humans to the viruses thought to be responsible for animal tumors.

The closest link detected thus far between human neoplasia and a virus involves Burkitt's lymphoma and nasopharyngeal carcinoma, two histologically and epidemiologically distinct tumors, and the Epstein-Barr virus (EBV). Seroepidemiologic, tissue culture and nucleic acid studies suggest that EBV plays a significant role in

the etiology or development of these tumors.

EBV is the widespread herpes-type virus which was first detected in lymphoid cell lines derived from an African patient with Burkitt's lymphoma. There is compelling epidemiologic evidence that EBV is an etiologic agent of infectious mononucleosis(57). Moreover, there is some evidence which suggests that EBV plays a role in the genesis or development of Hodgkin's disease. In studies dealing with a combined group of over 900 Hodgkin's disease patients, the prevalence of antibody to EBV has been similar to that of controls. However, in most studies(32,58,59,60,A.S. Evans, unpublished data) the geometric mean titers of the Hodgkin's disease patients have been found to be significantly higher than those of the controls. Moreover, in the latter study no significant difference was found between patients and controls for antibody to measles, rubella or parainfluenza viruses, indicating that a generalized immunologic alteration was not causing the elevation of the titers to EBV. The significance of these observations is not known, and in hypothesizing a role for EBV in Hodgkin's disease it must be kept in mind that infection with this virus is common throughout the world and only an extremely small proportion of persons with a history of EBV infection ever develops Hodgkin's disease.

It is noteworthy, moreover, that in those studies in which a difference in EBV antibody titers was found, only 30-40% of the Hodgkin's disease patients had titers of 1:320 or greater, while more than 80% of patients with Burkitt's lymphoma and nasopharyngeal

carcinoma routinely are found to have titers of 1:320 or above(61,62). Furthermore, while nucleic acid hybridization studies have demonstrated the EBV genome in African Burkitt's lymphoma and nasopharyngeal carcinoma tissue(63,64), attempts to demonstrate the presence of EBV genome in tissue from patients with Hodgkin's disease have been unsuccessful(65).

The international variations in age-specific incidence rates of Hodgkin's disease for children and young adults are reminiscent of the variations in rates for paralytic polio during the years prior to the introduction of the polio vaccines. This suggests the hypothesis that first exposure to EBV during adolescence or adulthood results in an elevated risk for Hodgkin's disease, just as delayed exposure to polio virus places a person at high risk for paralytic disease. Under this hypothesis one would expect persons who develop EBV-related infectious mononucleosis after childhood to have an increased risk for Hodgkin's disease since these patients comprise a group whose exposure to EBV was delayed in comparison to that of the general population. A number of studies have been carried out to test this hypothesis. In a retrospective study of United States Army veterans with a documented history of infectious mononucleosis no increased risk for Hodgkin's disease was found(66). In contrast, a prospective study of veterans(67) and a Danish study involving a follow-up of over 17,000 patients with heterophile-positive infectious mononucleosis(68), showed a significantly increased incidence of Hodgkin's disease, in comparison to the same age groups in the general population. It should

be noted, however, that the age-specific incidence rates for infectious mononucleosis are positively correlated with socioeconomic status and that, as described above, socioeconomic status may be a determinant of Hodgkin's disease risk. Thus the increased risk for Hodgkin's disease observed among patients with a history of infectious mononucleosis may be attributable to the relatively high socioeconomic status of this segment of the general population.

In a retrospective study comparing 2,282 United States college students having a history of heterophile-positive infectious mononucleosis, and 2,779 students matched for age and sex and attending the same universities, no significant association between prior infectious mononucleosis and Hodgkin's disease was found (C.D. Carter, unpublished data). The patient and control groups presumably had the same socioeconomic status distributions, thus eliminating a possible bias in favor of the hypothesized association between infectious mononucleosis and Hodgkin's disease, but the low incidence of Hodgkin's disease makes the detection of an association in a study of this size extremely difficult.

At present there is no evidence associating Hodgkin's disease with viruses other than EBV or with nonviral agents. Although Hodgkin's disease patients have increased rates for tuberculosis and some fungal infections, it is thought that this is due to the immunologic changes described earlier which result in an enhanced susceptibility to these agents.

2. Seasonality of Clinical Onset

Conflicting evidence regarding the seasonal variation of clinical onset of Hodgkin's disease has been reported. An investigation of the dates of first manifestation of the disease in Gottingen, Germany, for Hodgkin's disease cases diagnosed between 1953 and 1967 showed a striking peak in the winter months, and the authors suggest exogenous factors, such as viral infections as the cause of the observed variation(69). This seasonal variation was not confirmed in a similar study done in Israel(70), and work done by Bjelke(71), based on the date of diagnosis, also failed to show a significant seasonal variation.

Analysis of this question is complicated by the difficulty of establishing the date of onset of clinical manifestations and also by the variable length of time between the biologic beginnings and the onset as perceived by the patient. The issue is obscured further if one hypothesizes a role for an infective agent, since it may affect the date of clinical onset either by triggering the neoplastic growth or by influencing its development.

3. Month of Birth

The month of birth of patients with Hodgkin's disease has also been studied. In view of the fact that the incidence of human infection for numerous viruses varies in recurring yearly cycles, and since there is a correlation between occurrence of cancer in laboratory animals and their infection with viruses at an early age, the elevated prevalence of certain birth-months among Hodgkin's disease patients could be taken as evidence supporting the hypothesis

of a viral etiology for the disorder. In a study of children dying of Hodgkin's disease under the age of 15 years in the United States between 1960 and 1964, Fraumeni and Li(72) found significantly more than the expected number were born in July and August. Subsequent studies, however, failed to reveal a distribution of birth-months different from that expected(71,73).

4. Time-Space Clusters of Hodgkin's Disease Cases

The occurrence of clusters of cases of a particular disease suggests the influence of transitory environmental factors, such as an infective agent, in the etiology of the disease. There have been several reports of clusters of Hodgkin's disease cases(71,74,75). In the latter report, Vianna et al. described a series of 34 lymphoma cases, 31 of which were Hodgkin's disease, in Albany County, New York, which were interlinked over a 20-year period. There were nine instances of case-to-case contact, and 25 instances of case-contact-case interaction. The authors interpret these findings as evidence that Hodgkin's disease was transmitted either case-to-case or through some healthy carrier. The significance of these findings was questioned by Pike and Smith(76), who viewed the statistical methods and choice of controls in the Albany study as being inappropriate, and pointed out that even in the case of diseases with a low incidence, "statistically significant" clusters can be expected to occur periodically when a large population is at risk. Pike and Smith also called attention to the studies done in England(77) and the United States(78) in which the patient populations investigated were not chosen because of a previously recognized cluster of cases,

and in which no statistically significant clusters were found.

5. Family Studies

Numerous family studies have been done to assess the risk for Hodgkin's disease of relatives of patients with this disorder(79,80). Razis et al.(29) estimated the risk of first degree relatives of Hodgkin's disease patients to be three times that of the general population, and interpreted the similarity of dates of onset of Hodgkin's disease in different family members, regardless of age, as evidence for the importance of non-hereditary and perhaps infectious factors in the etiology of the disease. Similarly, Vianna et al.(81) reported that among 23 pairs of first degree relatives with Hodgkin's disease studied in New York State, the time intervals between diagnoses were shorter than the age differences between the family members. Blot(82) commented on the difficulty of interpreting the findings of these two studies and concluded that they cannot be accepted as evidence favoring an environmental factor in familial Hodgkin's disease.

Creagan and Fraumeni(83) described the pedigree of an Anglo-Saxon family which featured the aggregation of Hodgkin's disease in three siblings and an aunt, two cases of idiopathic thrombocytopenia purpura, one with Hodgkin's disease, and one case each of monocytic leukemia, regional enteritis, breast cancer and congenital anomalies. This array of diseases suggested to the authors that a genetically determined disorder of immunological response with diverse clinical manifestations was responsible for the cluster of Hodgkin's disease cases.

In a recent study Grufferman et al.(84) found that siblings of young adult patients with Hodgkin's disease have a seven-fold excess risk of developing the disease. In view of this elevated relative risk and the high sex concordance of Hodgkin's disease sibling pairs found in this and other studies, the authors concluded that the excess cases among the siblings are due to either interpersonal transmission of an etiologic agent or to common-source exposure.

In summary, the investigations done to date have not provided any conclusive evidence in favor of the hypothesis that an infectious agent is involved in the genesis of Hodgkin's disease. Seroepidemiological studies have shown that Hodgkin's disease patients more frequently have an unusually high and specific antibody response to EBV than do controls. The significance of this finding is not known. Familial studies have revealed that first degree relatives of Hodgkin's disease patients have a several-fold higher risk for developing the disease when compared to population controls, but this must be viewed in light of the fact that an extremely small proportion of patients with Hodgkin's disease have a close relative who also has the disease. In view of these findings, it would seem prudent to conclude that if an infectious agent is involved in the etiology of Hodgkin's disease, it must be a common agent with a low oncogenic potential.

IV. Methods

a. The Setting

The present study was carried out in São Paulo, Brazil, at the Hospital A.C. Camargo (HACC), which is a publicly-funded, 500-bed institution which deals exclusively with the diagnosis and management of neoplastic disease. HACC is a modern, well-equiped hospital which provides medical care at a sophisticated level. It is also a training center with a large house staff and is affiliated with the University of São Paulo Medical School. Approximately 4,500 new patients are seen at HACC per year and nearly 60 percent of these patients are found to have neoplastic disease. During 1974 there were over 55,000 outpatient visits and 5,600 admissions. Since HACC opened in 1953 over 800 cases of Hodgkin's disease have been diagnosed. Approximately 250 patients with Hodgkin's disease are actively followed as outpatients, and in recent years an average of 65 new cases of Hodgkin's disease have been diagnosed per year.

HACC is a referral center which receives patients from a large catchment area. Forty-three percent of the patients come from Greater São Paulo, 39 percent from São Paulo State outside of the capital, and 18 percent come from other states in Brazil(85). While most patients are referred to HACC by physicians, many come to the hospital directly for their first contact with the health care system.

Patients at HACC are divided into three groups according to their ability to pay for the medical care they receive. Private, self-paying patients are cared for in clinic and inpatient

facilities which are physically separated from the rest of the hospital, and our group had no access to these patients or their records. Information relating to these patients is not included in the hospital utilization and diagnosis statistics presented above. The second group consists of patients whose care is paid for by the national health insurance program administered by the Instituto Nacional de Prevedência Social (INPS). A third group is made up of charity patients who are treated without charge. Approximately 55 percent of the non-private patients at HACC are in this latter category.

b. Selection of Study Subjects

Seventy Hodgkin's disease patients were included in this study, all of whom received care as outpatients or were hospitalized at HACC during the study period (June-September, 1976). Sixty-two of the patients had had the histological diagnosis of Hodgkin's disease made at HACC, and the remaining eight had been referred to HACC after the histologic diagnosis was made at another institution. All of the patients at one time had been hospitalized at HACC, and only INPS or charity patients were included in the study group. No selection criteria based on age, year of diagnosis, stage of disease, sex or therapeutic history were employed.

This study of Hodgkin's disease uses two comparison groups. The first is a group of 70 controls, matched for sex and age within one year, who were hospitalized or had a clinic visit at HACC during the study period. None of the controls had Hodgkin's disease or lymphoma. Sixty-four controls had malignant neoplasms

and six had benign neoplastic disease. Thirty different disease classifications were represented in the control group. All controls had been inpatients at one time at HACC and only INPS or charity patients were included in the control group. The procedures used to locate the Hodgkin's disease patients and controls at HACC were identical, with the exceptions that the matching criteria were applied in selecting the latter group and the patient diagnoses sought for the two groups were different.

The second comparison group in this study is made up of 139 siblings of the Hodgkin's disease patients. No selection or matching criteria were applied to the siblings. All siblings who accompanied a Hodgkin's disease patient on an out-patient visit or visited a hospitalized Hodgkin's disease patient at HACC during the study period were accepted for this comparison group. In addition, many siblings residing in Greater São Paulo were interviewed in their homes as time and public transportation permitted. It should be noted that all Hodgkin's disease patients, controls and siblings whose cooperation was solicited agreed to become participants in the study.

c. Description of the Interview Schedule

The method chosen for obtaining information from the study participants was an interview schedule to be administered directly to each person by one of the two investigators. A complete interview schedule is presented in the Appendix. This method was viewed as the only effective alternative for several reasons. Most importantly, many of the study subjects were illiterate, or nearly so,

and could not have completed a self-administered questionnaire. Furthermore, most of the information sought was not dichotomous in nature and often it was necessary for the interviewer to interpret the questions for the study participant. Finally, telephone interviews were not possible since very few of the participants had telephones in their homes.

Each interview was conducted by this author or the research associate, both of whom spoke fluent Portuguese and conducted the interviews in the native language of the study participants. In most cases the Hodgkin's disease patient and matched control were interviewed by the same investigator. Study subjects were rarely interviewed alone. In the case of adult participants a spouse or blood relative was usually present and often provided useful information when the knowledge or recall of the interviewee was deficient. When the study subject was a child or adolescent, the mother, or occasionally the father or an older sibling, was the informant.

The following paragraphs contain commentary on the interview schedule questions, the medical record data obtained, the hypotheses which were being tested in each case and the transformation and selection of data done in preparation for the statistical analyses.

Each patient's place of residence was recorded as the premorbid address given at the time of the first visit to HACC, and place of birth was also recorded. This information was obtained to permit a statistical comparison of the geographic distribution of the Hodgkin's disease and control groups, and also to define the geographic distribution of the Hodgkin's disease group, so that an appropriate population structure could be chosen for the calculation

of the incidence function curve which will be described in Section d. of this chapter.

The age and sex of each Hodgkin's disease patient was recorded to permit the calculation of age specific and total sex ratios which are necessary for the determination of the epidemiologic pattern of the disorder among these patients. Moreover, the age data are necessary for the calculation of the incidence function curve. The histologic subtype recorded was that listed on the pathology report for the first adequate biopsy, and this information is also a determinant of the epidemiologic pattern.

The study participants were asked if they had had a tonsillectomy or "an operation in their throat," in order to test the hypothesis that tonsillectomy is a risk factor for Hodgkin's disease. In addition, the Hodgkin's disease patients were asked to provide tonsillectomy information for all their siblings, including those who were not study participants, in order to increase the size of the sibling group for a separate analysis.

Questions relating to socioeconomic status were asked in order to test the hypothesis that there is a positive correlation between socioeconomic status and risk for Hodgkin's disease. Two indicators of socioeconomic status were studied: occupation and educational level. Current occupation was recorded for the Hodgkin's disease patients and the matched controls, or that of the person who provided financial support for the study subject in the case of children or others who were not employed. The occupations of the spouses were also determined, and the socioeconomic status of both

members of a married couple was taken to be that of the member who had the higher of the two. The occupation of the father or family breadwinner when the study subject was eight yours old was obtained as a means of assessing childhood socioeconomic status. In preparation for statistical analysis, a numerical value between one and 100 was assigned to each occupation using the Duncan Socioeconomic Index for Occupations(86).

The second variable related to socioeconomic status which was studied among the Hodgkin's disease patients and controls was educational level. Since the age at which a person leaves school, most commonly to work on the family farm or other family enterprise, is probably more strongly correlated with socioeconomic status than the actual grade level attained, the former was taken as the indicator of educational level. The educational level of the father and mother of each study participant was determined in a similar manner, as a measure of childhood socioeconomic status.

To assess sibship size and birth order, each Hodgkin's disease patient and control was asked to dictate a list of his siblings by age and sex, including only those who survived to their first birthday. Sibship size data is of interest in order to test the hypothesis that the degree of intimate exposure to other children influences the risk for Hodgkin's disease, possibly through increasing the probability of early infection with a transmissible agent which has either a protective or disease-potentiating effect. In addition, sibship size information is useful in determining if the increased risk for Hodgkin's disease associated with the other variables is

limited to sibships of a certain size. Birth order information was obtained to test the hypothesis that the presence or absence of predominantly younger or older siblings influences the risk of developing Hodgkin's disease.

The marital status of the Hodgkin's disease patients and controls was also obtained. A significant difference between the two groups might reflect differences in socioeconomic status, or the effects of an agent transmitted by intimate interpersonal contact. In the statistical analysis of this data, only those study subjects over 21 years of age were included.

An occupational history was taken from each Hodgkin's disease patient and control in the study. The interviewee was asked to describe by title, function and responsibility each job which was held for more than six months, including student and volunteer jobs. Subsequestly, each job was assigned an arbitrary code number which corresponded to that job classification in the Detailed Classification of the Bureau of the Census, 1950(86). Due to the fact that this classification list is quite detailed and includes more than 500 job classifications, and since we were investigating occupational history in order to detect environmental exposure which leads to an increased risk for Hodgkin's disease, the code numbers were grouped by type of exposure. For example, all occupations which involved exposure to wood and wood products made up one group and those involving exposure to natural fibers and textiles constituted another group.

To assess the effect of drug use on the risk for Hodgkin's disease, all study participants were asked if they had ever taken amphetamines, mentioned by generic and brand names, or any drugs for weight reduction. Two months was chosen as the minimum time period which was considered positive exposure. To assess exposure to diphenylhydantoin, study subjects were asked if they had ever taken medicine for epilepsy, convulsions, fits or migrane headaches, or specifically the drug Comital, which is the only preparation of diphenylhydantoin currently available in Brazil.

A number of questions were asked of the study participants which were chosen to provide information relevant to the hypothesized role of an infectious agent in the genesis or development of Hodgkin's disease.

In an effort to assess delayed exposure to EBV, study subjects were asked if they or any of their family members had had infectious mononucleosis. After several dozen interviews, it became clear that the people in our study were not aware of the existence of infectious mononucleosis as a disease entity. Due to the fact that there are no pathognomonic symptoms associated with this disease which could be described to each interviewee, the questions relating to infectious mononucleosis were deleted from the schedule.

In order to determine if low or high exposure to other children during childhood is a determinant of risk for Hodgkin's disease, the Hodgkin's disease patient and control groups were asked how many close friends they had played with regularly at age eight,

and how many children slept in their bedroom when they were five, eight and eleven years old.

To assess the importance of exposure to children during adulthood as a risk factor, information was obtained on the number of persons less than 13 years old residing in the same household when each study subject was 21 and 30 years old. In addition, Hodgkin's disease patients and controls were asked to state the number of children they had who had lived to the age of one year.

In view of the fact that the immunologic response of Hodgkin's disease patients to EBV is known to be different from that of controls, it is of interest to determine if these patients respond to other common viruses in an unusual fashion. To explore this question, the Hodgkin's disease patients and controls were asked whether and at what age they had had chicken pox and measles, the number of times they had been hospitalized for viral illnesses, and if they frequently had cold sores or fever blisters caused by herpes labialis. A minimum of one lesion per month was taken as a positive response for the latter. It is interesting to note here that in a recent São Paulo study Carvalho et al.(87) reported a high correlation between the patient-provided history of chicken pox and serum antibody to the virus. In view of this, we can assume that our chicken pox data, and probably that relating to measles as well, are reliable.

Another variable studied relating to the hypothesized infectious etiology for Hodgkin's disease was the month of diagnosis, which was obtained from the Hodgkin's disease patients' charts. The expected

number for each month was taken as the number of Hodgkin's disease cases divided by 12. This assumption of non-seasonality of total diagnoses at HACC is probably not valid, because a large proportion of the patients come from agricultural regions and they would be less likely to seek medical care for a chronic disease during the growing season than at other times of the year.

Lastly, in an attempt to identify a time-space cluster of Hodgkin's disease cases which could be taken as evidence for a common-source exposure or transmission of an agent which resulted in multiple cases, the patients were asked to list all schools they had attended by name and geographic location. Analysis of this information was carried out by first grouping the patients by location of school, and then searching the location lists for schools which were listed more than once. A comparison group for this aspect of the study was not developed.

d. Statistical Methods

A description of the statistical methods used to analyze the interview data obtained in this study is contained in the following paragraphs. The analysis was done at the Yale Computer Center on an IBM 360/70 electronic computer using SPSS programming language (Statistical Package for the Social Sciences).

Analysis of matched pairs data for polychotomous variables and of unmatched data for dichotomous variables was carried out using the chi square statistic of the form

$$\chi^2_{df} = \sum_{i=1}^{R} \frac{(f_i - F_i)^2}{F_i} \quad . \qquad \text{(88, pg. 238)}$$

For several of the dichotomous variables with unmatched data an estimate of the relative risk was calculated, as well as the confidence interval for this estimate. The cross-product ratio is a measure of the degree of the association between an antecedent factor and an outcome, and may be used as an approximation to the relative risk for data of the form

		Factor		
		A	$\bar{A}$	
Outcome	B	n_{11}	n_{12}	$n_{1.}$
	$\bar{B}$	n_{21}	n_{22}	$n_{2.}$
		$n_{.1}$	$n_{.2}$	$n_{..}$

where the relative risk is approximated under the rare disease assumption by the equation

$$\text{Relative Risk (RR)} \approx \text{Cross Products Ratio} = \frac{n_{11}\,n_{22}}{n_{12}\,n_{21}} .$$

(89, pg. 45)

The confidence interval for the estimated relative risk is given by

$$100(1-\alpha)\%\ \text{confidence interval} = \exp\{\ln(RR) \pm Z_{1-\frac{\alpha}{2}}(SE_{\ln RR})\}$$

where the standard error of the natural logarithm of the relative risk is calculated by using the formula

$$SE_{\ln RR} = \ln(RR)/\chi$$

having gotten χ^2 by the equation on page 45. The confidence interval

then takes the form

$$\exp\{\ln(RR)(1\pm Z_{1-\frac{\alpha}{2}}/\chi)\}$$

which is asymmetric about the estimate of the relative risk, as it must be, since the latter cannot take on a value less than zero(90). For significance the lower limit of the confidence interval must be greater than unity.

McNemar's test was used to analyze matched pairs for dichotomous variables with data presented in the form

Factor A		Controls: A	Controls: $\bar{A}$	
Cases: A		n_{11}	n_{12}	$n_{11}+n_{12}$
Cases: $\bar{A}$		n_{21}	n_{22}	$n_{21}+n_{22}$
		$n_{11}+n_{21}$	$n_{12}+n_{22}$	$n_{..}$

The chi square statistic in this case is given by

$$\chi^2 = \frac{(|n_{12}- n_{21}| - 1)^2}{n_{12}+n_{21}} \quad . \qquad (89, \text{pg. } 75)$$

It is of interest to note here that only those pairs which differ for the factor contribute to the test statistic. The concordant pairs are excluded from the calculation under the assumption that the matching has eliminated the effect of extraneous factors which cause non-concordance. The estimate of the relative risk is given by the approximation to the odds ratio

$$\text{Relative Risk (RR)} = \text{Odds Ratio} = \frac{n_{12}}{n_{21}}$$

and again the confidence interval is determined using the method of Miettinen given above.

In the case of matched pairs data for discrete and continuous variables, the matched pairs t-test was employed, using the test statistic

$$t_{df} = \frac{\bar{d}}{s_{\bar{d}}\, n^{1/2}}$$

where $\bar{d}$ is the mean of the differences between values of each pair, n equals the number of pairs and $s_{\bar{d}}$ is the standard error of the differences given by

$$s_{\bar{d}} = \frac{\Sigma d^2 - (\Sigma d)^2/n}{n - 1} \quad . \qquad \text{(88, pg. 121)}$$

The distribution of d is assumed to be normal, even though the distributions of the two samples may not be normal. This assumption is met provided that the variances of the two samples are not markedly different. For all analyses in which the matched pairs t-test was employed, the two-tailed probability was used to test for significance.

To analyze unmatched data for continuous variables the t statistic was also employed where

$$t_{df} = \frac{\bar{x}_1 - \bar{x}_2}{s_p\left(\frac{1}{n_1} + \frac{1}{n_2}\right)^{1/2}}$$

and the pooled estimate of the variance is given by

$$s_p = \{[(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2]/(n + n + 2)\}$$

(88, pg. 116)

In this case it is assumed that the two populations have normal distributions with the same mean and variance.

The age-specific incidence rates for Hodgkin's disease comprise one of the major indicators of the epidemiologic pattern of the disorder in a given population. The age-specific rates cannot be calculated using the data for the São Paulo Tumor Registry Hodgkin's disease patient group nor that of the present study because the populations at risk from which these cases were drawn are undefined. However, although the actual incidence rates cannot be calculated, the shape of the age-specific incidence curves can be estimated and inferences relating to the epidemiologic pattern may be drawn by utilizing the age-specific population data for São Paulo State and the rest of Brazil.

The shape of the incidence curve was estimated in the following manner. For each five-year age interval an "incidence function" was calculated, which is an unknown multiple of the actual age-specific incidence rate. This was done by dividing the percentage of the patient population for that group in the given age interval by the corresponding percentage of the hypothetical population at risk. In the case of the Tumor Registry group, the population census for São Paulo State for 1970(91) was used to calculate the denominators. For the Hodgkin's disease patient group in the present study, population percentage denominators were calculated by taking the average of the São Paulo State and total Brazil(92) population percentages for each interval, weighted according to the proportions of the study patients from São Paulo State and the rest of Brazil.

Summarizing

$$\text{Incidence Function}_{(x \to x+4)} = \frac{\%\text{ of patient group in interval}}{\%\text{ of hypothetical population at risk in interval}}$$

V. Results

Comparisons of the geographic distributions of the Hodgkin's disease patients and matched controls, done by state and region, for current residence and place of birth did not reveal any significant differences ($P > 0.25$ for all four tests).

The sex ratio for the 70 Hodgkin's disease patients in this study was 2.5 and the age-specific sex ratios ranging from 2.0 to 3.8 are shown in Table 1, accompanied by the values from several other studies for comparison.

The incidence function curves for five-year age intervals for the São Paulo Tumor Registry (1969-72) and the present study (1976) Hodgkin's disease cases are presented in Figure 4. The number of cases and the percent of the total group in each age interval are shown in Table 4. The denominator population percentages and the incidence function values for each age interval also are presented in this Table. Twenty of the patients in the present study were diagnosed during 1969-72 and thus are included in the Registry group.

The high degree of variability in the incidence function values for the Hodgkin's disease cases in the present study can be attributed to the relatively small sample size. This curve suggests that incidence rates increase with age and peak in the 45-59 age group. However, the sharp drop in rates for individuals older than 60 years would appear to be an artifact, assuming that people in this age group are less likely to seek treatment at HACC than are younger people.

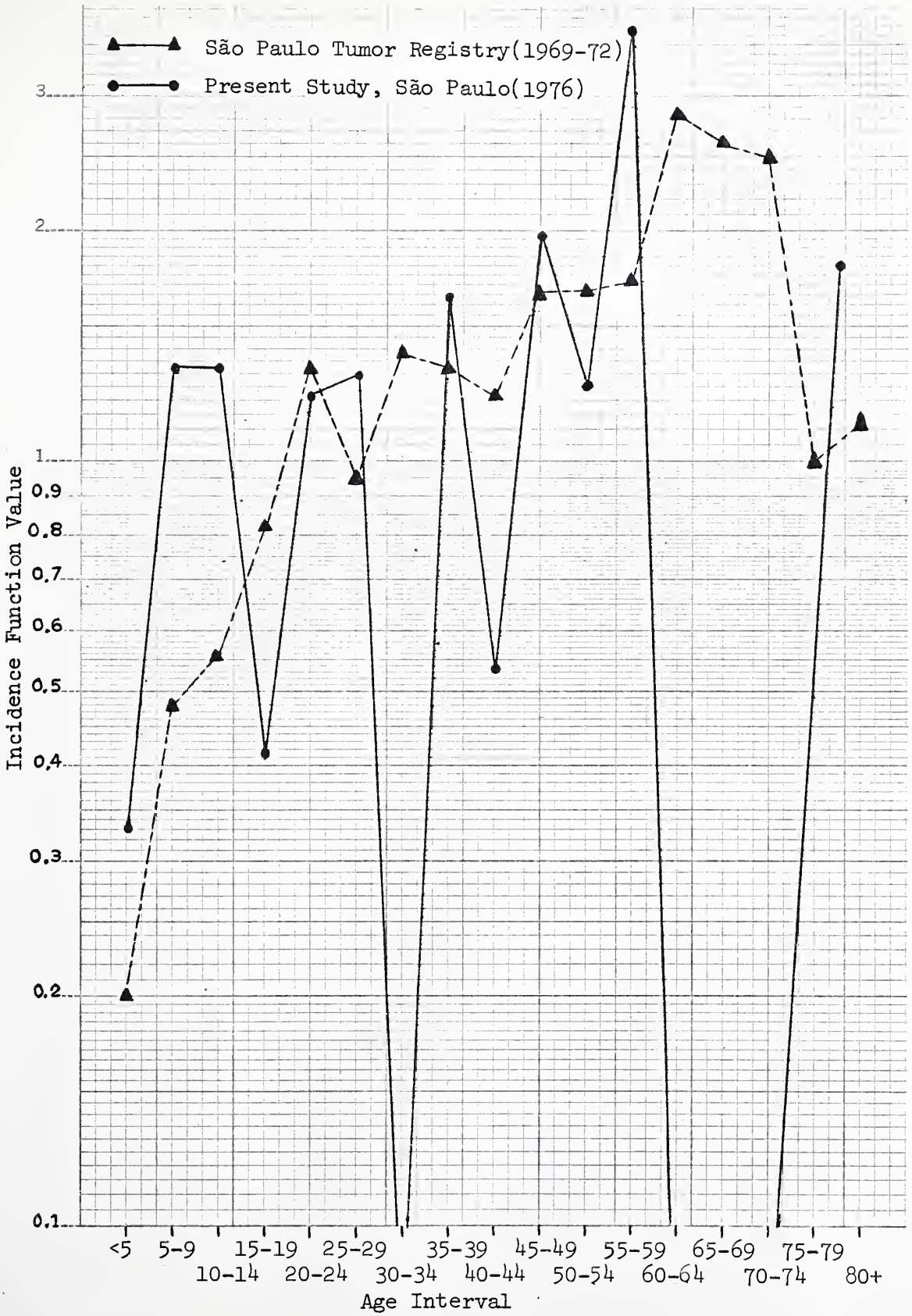

Figure 4. Hodgkin's disease in São Paulo, Brazil. Incidence function values by five-year age intervals for cases in the São Paulo Tumor Registry (1969-72) and the Present Study (1976).

Table 4. Hodgkin's disease in São Paulo, Brazil. Number of cases, percent of study group, percent of denominator population and incidence function values by age interval.

Data Source (year)		Age Interval								
		<5	5-9	10-14	15-19	20-24	25-29	30-34	35-39	→ next page
São Paulo Tumor Registry (1969-72)	N°	18	46	49	65	93	56	72	63	
	%	2.4	6.1	6.5	8.6	12.4	7.4	9.6	8.4	
population	%	12.2	12.7	11.7	10.5	9.4	7.9	6.9	6.4	
incidence function		0.20	0.48	0.56	0.82	1.32	0.95	1.39	1.33	
Present Study, São Paulo (1976)	N°	3	12	11	3	8	7	0	7	
	%	4.3	17.1	15.7	4.3	11.4	10.0	0	10.0	
weighted population	%	12.9	12.8	11.8	10.6	9.4	7.7	6.7	6.1	
incidence function		0.33	1.34	1.33	0.41	1.22	1.30	0	1.64	

Table 4. (Continued)

Data Source (year)		Age Interval								
		40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80+
São Paulo Tumor Registry (1969-72)	N°	52	55	44	36	47	29	19	4	5
	%	6.9	7.3	5.8	4.8	6.2	3.9	2.5	0.5	0.6
population	%	5.7	4.4	3.5	2.8	2.2	1.5	1.0	0.5	0.5
incidence function		1.21	1.66	1.66	1.71	2.82	2.60	2.50	1.0	1.12
Present Study, São Paulo (1976)	N°	2	6	3	7	0	0	0	1	0
	%	2.9	8.6	4.3	10.0	0	0	0	1.4	0
weighted population	%	5.5	4.3	3.4	2.7	2.1	1.5	1.0	0.5	
incidence function		0.53	1.98	1.25	3.64	0	0	0	2.8	

The Tumor Registry incidence function curve shows less variability and suggests a unimodal pattern, with a peak among the elderly 60-74 years of age. Again, the sharp drop in incidence rates beyond this peak probably is an artifact and does not represent the true pattern of incidence in this age group.

The distribution of the four histological subtypes by sex is presented in Table 2 in percentage form for the 62 Hodgkin's disease patients on whom this information was available. Comparison data from other studies is also presented in this Table. An analysis of the distribution of the subtypes by age interval (0-19, 20-49 and 50-79) revealed that the subtype proportions did not vary as a function of age ($\chi^2_8 = 4.11$, $P = 0.85$).

The comparison of the tonsillectomy histories of the Hodgkin's disease patients with those of the siblings who were interviewed or whose parent was the informant showed a significant association between the presence of Hodgkin's disease and prior tonsillectomy ($\chi^2_1 = 4.89$, $P = 0.03$). The estimated relative risk was 2.7, with a 95% confidence interval of 1.1 → 6.6. A summary of the tonsillectomy data for the total group and by sibship size is presented in Table 5. As in the case of the total group, a significant association between the presence of Hodgkin's disease and prior tonsillectomy was found among individuals from sibships of size six or greater ($\chi^2_1 = 3.78$, $P = 0.05$). The estimated relative risk was 4.0 for this group. In contrast, no increased risk was observed among tonsillectomized individuals from sibships of size five or less ($\chi^2_1 = 1.06$, $P = 0.30$). Further analysis of the tonsillectomy

Table 5. Tonsillectomy rates for Hodgkin's disease patients in the present study and siblings, by sibship size, with relative risk of developing Hodgkin's disease for tonsillectomized vs. non-tonsillectomized siblings.

	Tonsillectomy							
	Patients		Siblings					
Sibship Size	Proportion	Rate(%)	Proportion	Rate(%)	χ^2	P	Relative Risk	95% CI for Relative Risk
2-5	7/32	21.9	6/46	13.0	1.06	0.30	1.9	0.6 → 6.0
6+	5/38	13.2	3/82	3.7	3.78	0.05	4.0	1.0 → 16.0
All Patients	12/70	17.1	9/128	7.0	4.89	0.03	2.7	1.1 → 6.6

data by narrower sibship size ranges (e.g. 2-3, 4-5, etc.) was attempted, but the small number of tonsillectomized patients in each range precluded meaningful statistical inference. The mean ages of the Hodgkin's disease patients and the siblings were 27.4 and 22.2, respectively, and were significantly different ($t_{197} = 2.18$, $P = 0.05$). When this analysis was repeated for the patients and siblings less than 30 years of age, however, no significant difference was found ($t_{136} = 0.05$, $P = 0.50$). The sex ratio for the sibling group was 1.0, which is significantly less than that of the Hodgkin's disease patients ($\chi^2_1 = 9.0$, $P = 0.005$). However, analysis of data for the combined group of Hodgkin's disease patients and siblings showed that tonsillectomy rates for males and females were not significantly different ($\chi^2_1 = 0$, $P > 0.99$).

Tonsillectomy history data for siblings not interviewed which was obtained from the Hodgkin's disease patients was also tabulated. There were 222 siblings in this group, and only two were listed as having had the operation. Comparison of the one percent rate in this group with the 11 percent rate for the combined patient and interviewed siblings group suggests that the information provided by the Hodgkin's disease patients about their siblings was grossly incomplete, and no further analysis of data for this group of siblings was undertaken.

The socioeconomic status of the Hodgkin's disease patients, as measured by current occupation, was found to be significantly higher than that of the control group ($t_{69} = 3.38$, $P = 0.001$). Using Duncan's scale of one to 100, the mean socioeconomic status

values were 25.1 and 15.9 for the two groups.

In comparing the level of education of the Hodgkin's disease patients and controls as measured by the age at which schooling was terminated, it was found that the patients had significantly more education than the controls ($t_{69} = 3.59$, $P = 0.001$). The mean age at which the Hodgkin's disease patients left school was 9.2 years, and that of the controls was 7.6 years.

The childhood socioeconomic status data were compared for the Hodgkin's disease and control groups, using the socioeconomic value of the father's occupation when the study subject was eight years old, and no statistically significant difference was found ($t_{69} = 1.43$, $P = 0.16$). The mean childhood socioeconomic status value was 17.6 for the Hodgkin's disease patients and 14.4 for the controls. As a further assessment of childhood socioeconomic status, the educational levels, as defined above, of the parents of the Hodgkin's disease patients and controls were analyzed. No significant differences between the levels of the fathers ($t_{59} = 1.33$, $P = 0.19$) nor of the mothers ($t_{62} = 0.93$, $P = 0.36$) were found. The mean levels for the Hodgkin's disease patients' fathers and mothers groups was 7.0 years compared to 6.6 years for the controls' parents groups.

Analysis of sibship size for the Hodgkin's disease patients and the control group showed no significant difference ($t_{69} = 0.90$, $P = 0.37$), and the sibship size means for the Hodgkin's disease patients and the controls were 7.0 and 6.6 respectively. Assuming that in fact there is no difference between the two groups in sibship size, pair-wise analysis of the birth order was carried out, and no

significant tendency of the Hodgkin's disease patients to be born early or late in the birth sequence was found ($t_{69} = 1.50$, $P = 0.16$).

Comparison of the marital status for the Hodgkin's disease patients and controls over 21 years of age was done using three categories (yes, no and previously) and failed to reveal significant differences between the two groups ($\chi^2_2 = 0.57$, $P = 0.75$).

The occupational history information for the Hodgkin's disease and control groups was tabulated as described above. Thirty-eight of the Hodgkin's disease patients and 42 of the controls had ever worked. Only two of the exposure type classifications, woodworkers and textile workers, contained sufficient numbers of study subjects to warrant statistical comparison. Seven of the Hodgkin's disease patients had had occupational exposure to wood, compared to three of the controls. This difference is not significant ($\chi^2_1 = 1.40$, $P = 0.24$). Eight textile workers were found in each group. In all other exposure type classifications the numbers were small and the differences uniformly non-significant.

The prevalence of previous diphenylhydantoin and amphetamine use was quite low and differences between the Hodgkin's disease and the sibling groups was not significant. Four percent of the patients had used the former drug, compared to three percent of the siblings. Only one study subject was found to have taken amphetamines.

The questions which were asked to assess the degree of exposure to other children during childhood obtained information on the number of playmates at age eight, and the number of children sleeping in the same room when the study subject was five, eight and

eleven years old. The Hodgkin's disease patients were compared to the controls for these four variables, and no significant differences were found.

The questions dealing with exposure to children during adulthood ascertained the number of children each study subject had and the number of individuals less than 13 years of age who lived with the study subject at ages 21 and 30. No significant difference in the number of children was found between the Hodgkin's disease patients and controls ($t_{69} = -1.26$, $P = 0.21$). The number of people less than 13 years old living with the Hodgkin's disease patients at age 30 was not significantly different from that of the controls ($t_{26} = -1.55$, $P = 0.13$). However, comparison for the same variable at age 21 showed that significantly fewer people less than 13 years old lived with the Hodgkin's disease patients than with the controls ($t_{37} = -3.43$, $P = 0.001$).

Analysis of the data relating to the response to viral infections of the Hodgkin's disease patients and controls failed to detect any differences between the two groups. Comparisons of the prevalence of a history of measles and chicken pox, the age at which the study subjects had had these diseases, the rates of overt herpes labialis infections and the number of hospitalizations for viral illnesses, did not reveal any significant differences between the Hodgkin's disease patients and the control group.

A comparison of the frequency distribution of the month of diagnosis for the Hodgkin's disease patients with the calculated theoretical frequency did not show any significant pattern of seasonality.

Lastly, a tabulation of all the schools attended by the Hodgkin's disease patients did not reveal that more than one patient had attended any given school, and thus no time-space cluster was found.

VI. Discussion

Analysis of the geographic distributions of the Hodgkin's disease patients and controls in this study failed to show a significant variation between the two groups. Thus it is reasonable to assume that significant findings related to other variables which may be partially dependent on socioeconomic status are not attributable to geographic factors.

The epidemiologic pattern observed in this group of Hodgkin's disease patients is Type I, characteristic of developing countries in the tropics. This classification is supported by the unusually high percent of cases among children, with a high sex ratio, and a relatively high prevalence of the mixed cellularity and lymphocytic depletion subtypes (Tables 1 and 2). The incidence function curve for the study group (Figure 4) suggests a unimodal pattern of age-specific incidence rates with a peak among the elderly, and without the peak among young adults observed in Type II and Type III patterns. This age distribution is to be expected for the patients in the present study, since they were drawn only from the lower two of the three socioeconomic groups treated at HACC. The incidence function curve for the São Paulo Tumor Registry Hodgkin's disease cases (Figure 4) also is unimodal, with a peak among the elderly. Despite the fact that the patients in the Registry represent a broader socioeconomic spectrum than do the patients in this study, there is no early peak in incidence rates among young adults as was observed in the incidence rate curve for Recife, Brazil, presented in Figure 3. In view of the present study and Tumor Registry incidence

function curves, and the sex ratio and histologic subtype data from the former group, the epidemiologic pattern for Hodgkin's disease occurrence in São Paulo must be classified as Type I.

Our findings indicate that tonsillectomized individuals are at nearly a three-fold risk for Hodgkin's disease when compared to their siblings who have not had the operation. It appears unlikely that the significant disparity between the rates for the patients and siblings resulted from bias introduced through the use of this comparison group which was not matched for age and sex. While the sex ratios for the two groups were markedly different, further analysis showed that the tonsillectomy rates are not sex-dependent among the individuals we studied. The mean age of the Hodgkin's disease patients was significantly greater than that of the siblings, and this fact could be a source of bias because the siblings would have had, on the average, fewer years of exposure to the risk of tonsillectomy, and thus would be expected to have lower rates. However, when the comparison of ages is limited to patients and siblings under age 30, no age differences are noted. When this finding is viewed in the light of the fact that only two of the 21 tonsillectomized individuals in the combined Hodgkin's disease patient and sibling group were older than 30 years of age, the difference in mean ages for the two groups appears to be an unlikely source of bias. Moreover, it should be emphasized that the patients and siblings are matched for childhood socioeconomic status and family size, and both of these variables are determinants of tonsillectomy risk.

Bias in favor of the hypothesis that Hodgkin's disease patients have relatively high tonsillectomy rates could also be introduced by using siblings' tonsillectomy histories obtained from the patients, since an individual in the latter group is less likely to have knowledge about or to recall his sibling's tonsillectomy than his own. In previous studies(23,28) patient-provided information on sibling's tonsillectomy histories was included in the analysis. Our approach has been conservative in that we included in our analysis tonsillectomy data only from individuals who were actually interviewed, or whose parent was interviewed in the case of children, and thus eliminated the possibility of bias from this source.

The 2.7-fold risk for Hodgkin's disease found among tonsillectomized individuals is within the range of 0.7 → 3.6 found in the earlier investigations which were reviewed above. Our finding of elevated risk was somewhat unexpected, however, in view of previous studies done in populations with a relatively low prevalence of tonsillectomy history which failed to reveal an association between the operation and risk for the disease(22,26). Moreover, it is particularly surprising from a statistical point of view, given the overall tonsillectomy rate of 10 percent among the individuals we interviewed, that the increased risk was demonstrable in a study which included only 70 Hodgkin's disease patients and 128 siblings. From the apparent association of high overall tonsillectomy rates and the importance of tonsillectomy as a risk factor for Hodgkin's disease found in earlier studies(19,23,28), one could infer that

tonsillectomy affects Hodgkin's disease risk only in high socio-economic groups, that is, in developed countries with a Type III epidemiologic pattern. Our analysis of the tonsillectomy data broken down by sibship size showed that the increased risk is limited to large sibships (6+), which would appear to contradict the above inference since there is an inverse relation between socio-economic status and sibship size. This finding also does not agree with the results from the Boston study(28) which suggested that it is only in small sibships, particularly of size two, that the increased risk occasioned by tonsillectomy is observed.

In summary, the implications of the increased risk for Hodgkin's disease for tonsillectomized individuals observed in Brazil, which is a developing country with a Type I epidemiologic pattern for Hodgkin's disease and has a very low overall tonsillectomy rate, are not clear. Likewise, the meaning of the finding of increased risk only among large families is not readily apparent. If the association between tonsillectomy and increased risk for Hodgkin's disease observed in this study is in fact valid, one could speculate that the ablation of this lymphatic tissue modifies the manner in which the immune system interacts with an infectious agent with oncogenic potential. Assuming that tonsillectomy affects risk for Hodgkin's disease through a mechanism of this nature, it would be reasonable to expect risk to vary directly with sibship size, as was found in the present study, since the probability of a tonsillectomized individual's being infected with the hypothesized transmissible oncogenic agent would increase as the number of siblings increased. It should be pointed out, however, that

at most tonsillectomy plays a role in only a small proportion of Hodgkin's disease cases in a developing country such as Brazil, since the vast majority of Hodgkin's disease patients have not had the operation.

The finding of a significantly higher adult socioeconomic level among the Hodgkin's disease patients in this study in comparison to the controls is striking, especially in view of the highly significant results found when both current occupation and level of education were used as measures of socioeconomic status. Furthermore, it is noteworthy that the Hodgkin's disease patients and controls were selected in a manner which excluded patients from the upper end of the socioeconomic scale, and thus a bias was introduced which made it more difficult, from a statistical point of view, to detect any differences in socioeconomic status between the two groups, than it would have been had the private patients not been excluded from the study. As in the case of the findings relating to tonsillectomy, the implications of the association between high socioeconomic status and risk for Hodgkin's disease remain to be clarified, and that aspect of socioeconomic status which accounts for the increased risk among high socioeconomic groups remains obscure.

One could hypothesize that individuals with a high socioeconomic level tend to have delayed exposure to an infectious agent with oncogenic potential, and that this comparatively late primary infection results in a relatively severe host immune response, followed by an incomplete recovery characterized by persistent

immunological interaction between host and agent. In individuals thus affected, the oncogenicity of the agent would be more likely to be expressed. Alternatively, one could speculate that exposure to a non-infectious environmental agent is that aspect of socioeconomic status which accounts for the increased risk for Hodgkin's disease, but this would appear unlikely in view of the fact that the Type III nations, with a high level of socioeconomic development, do not have overall incidence rates greater than those of the Type I countries.

In view of the positive correlation between adult socioeconomic status and risk for Hodgkin's disease, the lack of an observed difference in childhood socioeconomic status between the Hodgkin's disease patients and controls further confounds the issue. However, one might consider that, due to the generally low socioeconomic levels of the study subjects, the detection of a difference between the two groups becomes even more difficult when childhood socioeconomic status is studied, since childhood socioeconomic status is almost invariably lower than adult socioeconomic status, and therefore it would be reasonable to conclude that an undetected difference actually may exist. This reasoning can also be applied to explain the lack of a difference in parents' levels of education.

The lack of significance in the analysis of the occupational histories of the Hodgkin's disease patients must be viewed as inconclusive, because the number of possible employment and exposure types is quite large in an industrialized society, and a study of only 70 individuals is statistically unlikely to detect any types of

exposure associated with a high risk for the disease.

Analyses of the responses to the questions prompted by the hypothesized role for an infectious agent in the etiology of Hodgkin's disease failed to provide insight which would permit the formulation of new, more incisive hypotheses. Childhood exposure to other children was found to be the same in the Hodgkin's disease patients and the control group. Thus it appears not to be the lonely child with few sibling and neighborhood playmates, whose delayed exposure during childhood to an infectious agent results in an increased risk for Hodgkin's disease during adolescence or adulthood. Exposure to children during adulthood was also found to be the same in the patients and controls, with the exception of a relatively smaller number of children cohabitating with the Hodgkin's disease patients at age 21. Most likely this finding is related to the lower socio-economic status of the controls which results in their remaining in an extended family situation until a later age. The implication of this lack of importance of exposure to children at any age is that if an infectious agent plays a role in the genesis of Hodgkin's disease, it is unlikely that children have a significant role in the transmission of the agent. The fact that a time-space cluster in a school was not found also supports this conjecture, although it should be kept in mind that in a study of 70 Hodgkin's disease patients drawn from a large geographic area, the finding of a cluster is extremely improbable.

Lastly, the lack of differences between patients and controls in responses to infections with common viral agents strengthens

the case for a role for EBV in the cause or development of Hodgkin's disease, since it confirms the specificity of the abnormal immune response to EBV observed in seroepidemiologic studies.

In conclusion, it has been found in the lower socioeconomic setting of a developing country that a relatively high socioeconomic status and tonsillectomy are risk factors for Hodgkin's disease. These findings confirm the results of several similar investigations carried out in the industrialized nations. Although the biologic significance of these findings are not clear, they do provide evidence in support of the hypothesis that the etiology of Hodgkin's disease is complex and affected by a number of factors. In future studies attention should be directed toward high risk subgroups of Hodgkin's disease patients, i.e. tonsillectomized patients and those with elevated socioeconomic status, in an effort to identify those aspects of these factors which account for the increased risk.

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VIII. Appendix: The Interview Schedule

ESTUDO de SAÚDE

Nome _____ Número _____

Endereço _____

Pais-idades-informante _____

A. Paciente Hospital _____
Registro _____

B. Irmão Paciente _____
Número _____

C. Contrôle Paciente _____
Número _____

1. Data _____
2. Entrevistador _____
3. Hora do início _____

Primeiro, quero perguntar algumas coisas gerais:

4. Onde nasceu? _____
cidade estado país

5. Em que ano nasceu?
ano

6. Quantos anos você estudou? anos
   a. Ainda estuda?
      1. SIM
      2. NÃO: Quando deixou de estudar?
ano

7. Qual é seu emprego atual? _____
   a. É casado?
      1. SIM: Qual é o emprego atual da esposa?
_____
      2. NÃO
      3. SEPARADO ou DIVORCIADO

8. Tem filhos?
   1. SIM: Quantos filhos tem?
   (Tabela: O mais velho é homem ou mulher? Quando nasceu? etc.)
   2. NÃO

Ordem de nasc.	Sexo	Mês de nasc.	Ano de nasc.
1º			
2º			
3º			
4º			
5º			
6º			
7º			
8º			
9º			
10º			

Veja o verso

Muito bem, agora quero fazer algumas perguntas sôbre sua infância.

9. Primeiro, tinha irmãos?
   1. Quantos eram ao todo? [ ]
      (Tabela: Qual foi o nome do mais velho, ou do que nasceu primeiro? Quando nasceu? etc.)

Ordem nasc.	Nome	Nasc. mês	Nasc. ano	Op. das amíg. sim	Op. das amíg. idade	Op. das amíg. não
1º						
2º						
3º						
4º						
5º						
6º						
7º						
8º						
9º						
10º						

[ ] Veja o verso

10. (Tabela acima) (Nome do irmão) foi operado das amígdalas?
    (Se sim) A que idade?

11. Quando você era menino, na sua casa moravam outras crianças, além dos seus irmãos, por mais de um ano?
    1. SIM: Quantas outras crianças moravam com sua família?
       (Tabela: Como se chamava o primeiro? Mais ou menos, quando nasceu? Durante quantos anos morou com vocês? etc.)
    2. NÃO

Nome	sexo	nasc.	anos na casa
1º			
2º			
3º			

[ ] Veja o verso

12. Durante sua infância você foi ao dentista?
    1. FREQUENTEMENTE
    2. COM REGULARIDADE
    3. DE VEZ EM QUANDO
    4. POUCAS VÊZES
    5. NUNCA

Agora, quero perguntar-lhe sôbre sua vida quando tinha 8 anos; isto foi em 19___ (calcule da questão nº 5).

13. Primeiro, quando tinha 8 anos (ou atualmente, se tem menos de 8 anos), em que tipo de casa morou?
    1. CASA COM 4 FAMILIAS OU MAIS
    2. " 3 " "
    3. " 2 " "
    4. CASA SÒMENTE DE SUA FAMILIA
    5. OUTRO TIPO: _____

    13a. A casa era de vocês, ou era alugada?
         1. ALUGADA 2. DE VOCÊS
    13b. A casa tinha quantos compartimentos? [ ]
    13c. A casa tinha algum sanitário?
         Quantos tinha? [ ]

14. Quando você tinha 8 anos (ou atualmente, se tem menos de 8 anos), quantas crianças moravam na sua rua, com quem você brincava pelo menos de vez em quando? [ ]

15. Quando tinha 8 anos (ou atualmente, se tem menos de 8 anos), seu pai ainda vivia?
    1. SIM: Qual era o emprego dele naquele tempo?

       _____

    2. NÃO: Qual era o emprego da pessoa que sustentava a casa?

       _____

16. Quantos anos, mais ou menos, seu pai frequentou a escola? [anos]

17. Quantos anos, mais ou menos, sua mãe frequentou a escola? [anos]

18. Quando tinha 8 anos (ou atualmente, se tem menos de 8 anos), quantas crianças dormiam no mesmo quarto com você? [ ]

19. Três anos depois, em 19____, quando tinha 11 anos, quantas crianças dormiam no mesmo quarto que você? [ ]

20. Quando tinha 5 anos, em 19____, quantas crianças dormiam no mesmo quarto com você? [ ]

21. Na sua infância, você foi alguma vez dormir em barraca ou debaixo de árvore no campo?
    1. SIM: Durante a infância você chegou a dormir mais de 4 semanas ao todo no campo?
       1. SIM: Mais de 8 semanas? 1. SIM 2. NÃO
       2. NÃO
    2. NÃO

22. Antes de começar ir para o jardim de infância, você frequentou um parque-infantil?
    1. SIM: Por mais de um ano? 1. SIM 2. NÃO
    2. NÃO

23. Tabela: Qual era o nome do jardim de infância e/ou da escola primária que você frequentou? Onde ficava? Até que ano você frequentou lá? etc.

Ano	Nome da escola	Cidade	Estado
J-Inf			
1ª			
2ª			
3ª			
4ª			
5ª			
6ª			
7ª			
8ª			
1º			
2º			
3º			

24. Em 19___ quando você tinha 21 anos, com quem morava?
1. ESPOSA OU FILHOS
2. AMIGOS
3. COM OS PAIS
4. SOZINHO
5. NUMA CASA DE ESTUDANTES
6. OUTRA SITUAÇÃO _____

24a. Quantas outras pessoas moravam com você? ☐

Destas, quantas tinham menos de 21 anos? ☐

Quantas tinham menos de 13 anos? ☐

25. Em 19___ quando tinha 30 anos, com quem morava você?
1. ESPOSA OU FILHOS
2. AMIGOS
3. COM OS PAIS
4. SOZINHO
5. NUMA CASA DE ESTUDANTES
6. OUTRA SITUAÇÃO _____

25a. Quantas outras pessoas moravam com você? ☐

Destas, quantas tinham menos de 21 anos? ☐

Quantas tinham menos de 13 anos? ☐

26. Alguma vez você tomou algum remédio para controlar ataques, convulsões, epilépsia ou enxaquecas?
1. SIM: Como era o nome do remédio que tomava? _____

Quando começou tomar êste remédio? ☐ ano

Ainda toma?
1. SIM
2. NÃO: Mais ou menos, quando deixou de êste remédio? ☐ ano

Quantos anos no total você tomou êste remédio? ☐ anos

Você tomava êste remédio regularmente (pelo menos uma vez por mês) ou de vez em quando?
1. REGULARMENTE 2. DE VEZ EM QUANDO

2. NÃO

27. Você tomou alguma vez dexedrina ou amfetamina regularmente para emagrecer ou por outras razões?
1. SIM: Como era o nome do remédio que tomou? _____
Quando começou tomar êste remédio? ☐ mês ☐ ano

Ainda toma?
1. SIM
2. NÃO: Mais ou menos, quando deixou de tomá-lo? ☐ mês ☐ ano

Você tomou o remédio durante quantos mêses? ☐ mêses

2. NÃO

28. Você já teve catapora (varicela)?
1. SIM: Com que idade? ☐ anos
2. NÃO
3. NÃO SABE

29. Teve sarampo?
1. SIM: Com que idade? ☐ anos
2. NÃO
3. NÃO SABE

30. Teve rubéola ou sarampo alemão?
1. SIM: Com que idade? [ ] anos
2. NÃO
3. NÃO SABE

31. Já foi hospitalizado por causa de uma infecção por virus (ou quando teve varicela sarampo ou rubéola?)
1. SIM: Motivo _____
Foi hospitalizado mais de uma vez? 1. SIM 2. NÃO
2. NÃO

32. Seus pais foram hospitalizados por causa de infecções de virus?
1. SIM: _____ pai/mãe
2. NÃO
32a. Irmão(s)?
1. SIM: _____ nome(s)
2. NÃO
32b. Irmã(s)?
1. SIM: _____ nome(s)
2. NÃO

33. Você já teve, repetidas vêzes, bolhas de febre (Herpes labial, Herpes febril) ou úlceras nos lábios?
1. SIM
2. NÃO

34. Já teve mononucleose infecciosa?
1. SIM. Com que idade? [ ] anos Foi hospitalizado? 1. SIM 2. NÃO
2. NÃO
3. NÃO SABE
34a. Algum irmão ou irmã já teve mononucleose infecciosa?
1. SIM: _____ nome Quando? [ ] ano
2. NÃO
34b. (Se é casado) Sua esposa já teve mononucleose infecciosa?
1. SIM: Quando? [ ] ano
2. NÃO
3. NÃO SABE
34c. (Se tem filhos) Algum de seus filhos já teve mononucleose infecciosa?
1. SIM: _____ nome Quando? [ ] ano
_____ nome Quando? [ ] ano
2. NÃO
3. NÃO SABE

35. Você já teve algum emprego em que trabalhava com madeira ou beneficiamento de madeira?
1. SIM: Que tipo de emprego foi? _____
Durante quantos anos trabalhava neste emprego? [ ] anos
2. NÃO

36. Já fez obras de madeira ou móveis de madeira sòmente para passar o tempo?
1. SIM: Ao todo durante quantos anos? [ ] anos
2. NÃO

37. Muito bem, estamos terminando. Ainda quero lhe perguntar alguma coisa sôbre os empregos que você já teve.

Primeiro, você teve emprego que durou pelo menos 6 mêses quando ainda estudava?
1. SIM: Veja a folha anexa "Emprego de Estudante"
2. NÃO

39. Você teve emprego depois de deixar de estudar?
1. SIM: Veja a folha anexa "Emprego"
2. NÃO

48. Já fêz algum trabalho como voluntário por um período de mais de 6 mêses, como por exemplo ajudar na igreja, sindicato ou centro social, clube de jovens, etc.?
1. SIM: Veja a folha anexa "Trabalho come Voluntário"
2. NÃO

50. Hora em que terminou _____

51. Tempo decorrido entre a última refeição e a retirada de sangue _____

52. Qualidade das informações obtidas
1. ELEVADA 2 MÉDIA 3. FRACA

Dia e hora para voltar se for necessário _____

Repassar o questionário _____

Lista de perguntas _____

Sangue _____

Autorização _____

"Emprego"

Nome _____

Nº _____

____ Qual foi o emprego que você teve?

a. Quando começou a trabalhar nisto? [/] mês ano

b. Quando deixou êste emprego? [/] mês ano

c. O que fazia quando trabalhava lá? _____

d. Nêste emprego você foi exposto a gases, vapores ou fumaça?
   1 SIM: Com que tipo de gás ou fumaça teve contato? _____
   2. NÃO

e. No seu trabalho, você ficava sempre exposto a grande quantidade de poeira ou pó de serragem?
   1. SIM: Como foi o contato? _____
   2. NÃO

f. No trabalho tinha que passar muito tempo entre crianças ou adolescentes?
   1. SIM: Como era o contato? _____
   2. NÃO

g. Trabalhava o dia todo ou sòmente uma parte do dia?
   1. TEMPO INTEGRAL 2. TEMPO PARCIAL

- -

____ Qual foi o emprego que você teve?

a. Quando começou a trabalhar nisto? [/] mês ano

b. Quando deixou êste emprego? [/] mês ano

c. O que fazia quando trabalhava lá? _____

d. Nêste emprego você foi exposto a gases, vapores ou fumaça?
   1. SIM: Com que tipo de gás ou fumaça teve contato? _____
   2. NÃO

e. No seu trabalho, você ficava sempre exposto a grande quantidade de poeira ou pó de serragem?
   1. SIM: Como foi o contato? _____
   2. NÃO

f. No trabalho tinha que passar muito tempo entre crianças ou adolescentes?
   1. SIM: Como era o contato? _____
   2. NÃO

g. Trabalhava o dia todo ou sòmente uma parte do dia?
   1. TEMPO INTEGRAL 2. TEMPO PARCIAL

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